Subantimicrobial Dose Doxycycline for Acne and Rosacea

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Acne vulgaris and rosacea present therapeutic challenges due to their chronicity, potential for disfigurement, and psychosocial impact. Although pathophysiologically distinct, both conditions have major inflammatory components. Consequently, topical and systemic antimicrobial agents are routinely prescribed for extended periods. Emergence of resistant strains of Propionibacterium acnes, adverse events, and compliance issues associated with chronic systemic tetracycline use have led to new treatment approaches. At subantimicrobial doses, tetracyclines reduce inflammation via anti-collagenolytic, antimatrix-degrading metalloproteinase, and cytokine down-regulating properties. Subantimicrobial dose (SD) doxycycline (Periostat 20 mg) has clinical utility in periodontitis and has been investigated in a double-blind, placebo-controlled trial in the treatment of moderate facial acne as well as in an open label study in the treatment of rosacea. The results of subantimicrobial dose doxycycline treatment in early trials support its benefits and further investigation in acne and rosacea. (SKINmed. 2003;2:234–245)

Acne vulgaris is the most common chronic skin disorder in the United States, affecting approximately 80% of persons at some point between 11 and 30 years of age.[1] In 1996 in the United States, the National Health Interview Survey reported the prevalence of acne was 26/1000 in persons <45 years of age.[2] Although the data in adults are sparse, one community-based study in England found the prevalence of clinical acne in women >25 years was 12% and in men it was 3%.[3] In addition to the economic costs of physician visits,[4] medications, and over-the-counter treatments,[5] the disfigurement and permanent scarring from acne can also have an adverse impact on psychosocial development and the quality of life of those who suffer from it.[1]

Rosacea is also a common, chronic dermatosis estimated to affect at least 1 in 20 people in the United States.[6] The majority are fair-skinned, Caucasian women, aged 30–50 years old.[7] One community study found 10% of those examined had rosacea (14% were women, 5% were men).[8] Similar to acne, rosacea has a significant economic cost[6] and psychosocial impact. Because the features of rosacea are so visible, people with rosacea are often distressed and embarrassed about their appearance and may exhibit low self-esteem.[9]

The Pathogenesis of Acne

Acne, the major disorder of the pilosebaceous unit, presents as noninflammatory (closed and open comedones) and inflammatory (papules, pustules, nodules) lesions. Several factors contribute to the pathogenesis of acne including androgens (testosterone and DHEA-S), increased sebum production, *P. acnes*-driven inflammation, and abnormal follicular epithelial differentiation. Desquamated cornified cells of the upper canal of the follicle become abnormally adherent. Instead of undergoing normal shedding and discharge through the follicular opening, the cells form a microscopic hyperkeratotic plug (the microcomedo) in the follicular canal, which enlarges and becomes a visible comedo. Inflammation (and subsequently, inflammatory acne) is a direct or indirect result of the proliferation of *P. acnes*. Overgrowth of this anaerobic organism, which is otherwise a normal constituent of the skin flora, occurs in the lipid-rich environment of the pilosebaceous units containing microcomedones. The host inflammatory response to *P. acnes* causes

damage to and rupture of the follicular wall which extends the inflammatory process into the surrounding dermis, resulting in the formation of the inflammatory lesions (papules, pustules, and nodules) and ultimately, destruction of the collagen matrix in the skin and cyst formation. Each of these pathogenic processes is a potential target for treatment.[1,10]

The Pathogenesis of Rosacea

Rosacea is a chronic, cutaneous vascular disorder. The earliest manifestations are increased and prolonged flushing, erythema, and sensitive skin. Although the etiology of rosacea remains unclear, local irritants (e.g., certain topical medications, astringents), wind, temperature extremes, hot and/or spicy foods and beverages, and alcohol can precipitate vasodilation (flushing) and inflammation (papules, pustules), the clinical signs of rosacea.[11] In addition, the erythema of rosacea is apparently aggravated by chronic sun exposure and photo damage. Exposing facial skin to sources of radiant heat, such as from a fireplace, reproduces the erythema.[12]

Extravascular fluid from the flushing reaction accumulates in the superficial dermis faster than the lymphatic vessels can remove it, leading to edema and damage to the lymphatic vessels. Elastin degeneration due to actinic exposure is probably a common cause of lymphatic failure. The upregulation of proteolytic activity during inflammation, along with neutrophil infiltration, exacerbates the degradation of elastin. Neutrophil elastase and gelatinase, from a variety of cellular sources, are capable of degrading the type IV collegen in the extracellular matrix on which the integrity of the capillary cell wall depends.

Lymphatic failure results in a sustained inflammatory response. In a later vascular stage, telangiectasias commonly develop on the nose, nasolabial folds, and cheeks. The condition progresses to an inflammatory stage characterized by erythematous papules and pustules on the cheeks, forehead, nose, and chin. The final stage is the development of large inflammatory nodules and connective tissue hypertrophy and fibroplasia (a result of the accumulation of plasma proteins). Finally, the fibroplasia may lead to the development of rhinophyma (predominantly in men).[11]

Commonly Used Therapy for Acne and Rosacea

Treatment for acne focuses on the resolution of inflammation, downregulation of sebum production, and elimination of the noninflammatory lesions manifested as microcomedo and comedones. In rosacea, therapy is typically anti-inflammatory in nature. For acne, the choice of therapy usually depends on the grade and severity. Rosacea therapy is determined by the stage.[11]

Mechanism of Action of Antimicrobials in Acne. The multifactorial nature of acne ideally requires an agent with a variety of mechanisms, exerting an effect not only on the bacteria but also on the inflammatory host response induced by the bacteria.[1] Certain antimicrobials exhibit these pleiotropic effects both reducing the numbers of bacteria and suppressing the host's inflammatory response. For example, tetracyclines have been shown to: diminish polymorphonuclear neutrophil (PMN) chemotaxis (possibly by inhibiting PMN chemotactic factor); reduce lipase production in *P. acnes*, resulting in a reduction of fatty acids in sebum on the skin surface;[13,14] affect complement pathways; down-regulate inflammatory cytokine production; and inhibit host collagenolytic activity. These pleiotropic properties have led to the widespread use of tetracyclines for the treatment of acne.

> "Tetracyclines diminish PMN chemotaxis, reduce lipase production in P. acnes, down-regulate inflammatory cytokine production, and inhibit host collagenolytic activity."

Systemic Antimicrobial Therapy

Systemic antimicrobial therapy is generally more effective than topical therapy presumably because the drugs penetrate the follicle more readily. Oral antimicrobials are indicated for persons with moderate-to-severe acne, persons with inflammatory acne in whom topical antimicrobials have failed or are not tolerated, persons with involvement of the skin of the shoulders, back, or chest (where it is difficult to apply topical therapy), and persons with mild-to-moderate acne who have a potential for substantial scarring or pigmentary changes (post inflammatory hyperpigmentation).[10]

The most common oral antimicrobials used are tetracycline HCl, doxycycline, and minocycline. The selection of an antimicrobial is typically

guided by the drug's efficacy, safety, convenience of use, and cost. The pharmacologic properties of doxycycline and minocycline are improved over tetracycline HCl. They both have improved absorption from the gastrointestinal (GI) tract along with increased lipophilicity resulting in better uptake by the pilosebaceous unit, and thus better tissue penetration than tetracycline HCl. In addition, their increased half-life allows once- or twice-daily dosing, potentially facilitating patient adherence to the dosing regimen.[15]

Efficacy of the Tetracyclines in Acne Vulgaris

There are few well done, placebo-controlled clinical trials evaluating the systemic use of tetracyclines (especially doxycycline) for the treatment of acne. Many studies lack objective descriptions of baseline disease severity and consistent measures of efficacy and outcome between studies, thus making the assessment of the relative efficacy of the study drugs even more difficult. Despite limitations, overall study results and numerous case reports support the use of the tetracycline family of drugs in the treatment of acne. These studies are summarized in Tables I and II.

Efficacy of Tetracyclines in Rosacea

Therapy for rosacea usually consists of a combination of topical and oral antimicrobials.[11] Papules and pustules in rosacea are generally eliminated with systemic antimicrobials, such as tetracycline HCl, and remission can be maintained to some extent with topical treatment, such as metronidazole.[16] Approximately 25% of patients relapse within 1 month after discontinuation of active therapy, approximately 50% to 60% at 6 months, and approximately 70% by 1–4 years in the absence of maintenance therapy.[16,17] The literature concerning rosacea is even more sparse than that of acne, but Table III summarizes some of the few comparative studies that have been done with tetracyclines in rosacea.

Drawbacks of Long-Term Standard Dose Therapy

The Problem of Resistance. The widespread use of oral antimicrobials for long-term acne therapy has resulted in the development of resistant strains of *P. acnes*. There is a clear association between the emergence of resistant *P. acnes* and the therapeutic use of these antimicrobials.[18,19] Resistance of *P. acnes* to tetracyclines increased with the duration of antimicrobial consumption,[20] demonstrating the effect of an antimicrobial regimen of tetracycline use in acne therapy on bacterial resistance.[21]

Overall resistance of *P. acnes* to antibiotics had increased from 20% in 1978 to 62% in 1996.[22,23] Levels of resistance to specific antibiotics vary widely, but strains resistant to erythromycin, clindamycin, tetracycline HCl, doxycycline, and trimethoprim are the most common.[18] The Minimum Inhibitory Concentrations (MICs) of tetracycline required to kill 50% of a population of *P. acnes* (MIC_{50}) are typically higher than MIC_{50} for doxycycline, which are typically higher than those of minocycline. Eady et al.[24] found that tetracycline-resistant organisms were cross resistant to doxycycline but susceptible to minocycline. Because resistance to minocycline was rarely observed, minocycline has been the preferred tetracycline for use in acne.[25] More recently, high-level resistance to minocycline (MIC_{50}, 4–16 μg/mL) has been found in populations in the United States.[26] While *P. acnes* resistance per se is not a major public health concern, the ability of microbes to pass resistance from one to another is well known, and even more important is the observation that resistance determinants can co-travel, resulting in the potential for spread of multiantibiotic resistance with potentially devastating effects in clinical practice.[12,27]

One strategy designed to minimize the development of resistance is to use a combination of topical and systemic therapies with regimens that incorporate agents with complementary mechanisms of action. Another innovative approach is to use a subantimicrobial dose (SD) of the antibiotic. As the predominant mechanism for the development of microbial resistance is selection of resistant strains over susceptible strains, a dose could be administered low enough that even susceptible strains remained unaffected. The exploitation of the anti-inflammatory properties of certain antibiotics might be sufficient to elicit a meaningful clinical response, and the administration of SDs may provide effective therapy without the risk of soliciting alterations in microbial susceptibility.

Other Adverse Consequences of Long-Term Tetracycline Therapy. Based on available information, there are more reports of serious adverse events associated with the use of minocycline than with tetracycline HCl or doxycycline. It is speculated that the difference is related to the unique metabolism of minocycline, which has

Table I: Efficacy of Tetracyclines in Acne Vulgaris—Minocycline vs. Placebo and/or Tetracycline

STUDY	DESIGN	EFFICACY MEASURES	RESULTS
Hersle, 1976 Minocycline vs. placebo; 43 pts (acne severity not specified)	DB, CO: Minocycline (n=18), 200 mg x 7 days; then 100 mg x 5 wk vs. Placebo (n=25) x 5 wk; then placebo group given minocycline and minocycline group given placebo x 5 wk	↓ Total acne load Lesions counted and graded (slightly modified) as in Juhlin study (Table II) After each period, new evaluation and new score expressed as % of original value	After 5 wks: ↓ total acne load: Minocycline ↓ 40%; Placebo ↓ 16% ($p<0.05$); After 2nd stage: Minocycline (CO) ↓ 37%; Placebo group ↓ 15% ($p<0.05$)
Hubbell, 1982 Minocycline vs. tetracycline; 49 pts, grade 2 or 3 pustular acne (Pillsbury system)	DB, 6-mo study Minocycline (n=25) 50 mg b.i.d. vs. Tetracycline (n=24) 250 mg b.i.d.	Conversion to grade 1 acne Grade 1=occasional profuse comedones, no inflammation Grade 2=comedones, small superficial pustules and inflammation Grade 3=comedones, small pustules, deeper inflammatory lesions	After 6 months: Reached and maintained grade 1 Minocycline: 23/25 (92%) Tetracycline: 18/24 (75%)
Leyden, 1982 Minocycline vs. tetracycline; 15 pts, moderately severe inflammatory acne	CO: 15 wk All pts tetracycline 500 mg b.i.d. x 6 wk; then 3 wk wash-out; then minocycline 100 mg b.i.d. x 6 wk	Effects of tetracycline and minocycline on *P. acnes* and skin-surface lipid levels: Complete count inflammatory lesions (face and trunk) Quantitative measure *P. acnes* on forehead and cheek (log mean *P. acnes*/cm²) Skin surface lipid levels (ratio FFA/trigly)	After 6 wks of tetracycline: Inflammatory lesions ↓ 52%; *P. acnes* on forehead ↓ 22%, cheek ↓ 27% ($p<0.05$); Skin surface lipids on forehead ↓ 87%, cheek ↓ 71% ($p<0.0001$ for both) After 2nd stage: Inflammatory lesions ↓ 60%; *P. acnes* on forehead ↓ 27% ($p<0.001$); cheek ↓ 30% ($p<0.001$); Skin surface lipids on forehead ↓ 70% ($p<0.001$); cheek ↓ 62% ($p<0.001$ for both)
Eady, 1990 Minocycline vs. tetracycline 25 pts (severity not specified)	6-mo study Tetracycline (n=12) 500 mg b.i.d. vs. Minocycline (n=13) 50 mg b.i.d.	Changes in numbers of *P. acnes* on skin surface (↓ $\log_{10}$ cfu/cm² skin); Resistance to both tetracycline and minocycline; Clinical improvement (mean % ↓ acne grade, Leeds technique)	After 12 wks: Minocycline ↓ *P. acnes* 10-fold >tetra ($p<0.02$) After 24 wks: Minocycline ↓ *P. acnes* 10-fold >tetra ($p<0.05$) No resistant *P. acnes* After 24 wks: Minocycline 56% ↓ acne grade Tetracycline 65.5% ↓ acne grade

pts=patients; DB=double-blind; CO=crossover; FFA=free fatty acids; trigly=triglyceride; sxs=symptoms; ↓=decrease.

Table II: Efficacy of Tetracyclines in Acne Vulgaris—Tetracycline vs. Doxycycline and Doxycycline vs. Placebo or Minocycline

STUDY	DESIGN	EFFICACY MEASURES	RESULTS
Juhlin, 1969 Tetracycline vs. doxycycline; 28 pts, moderate to severe acne	DB, CO T group: Oxytetracycline 250 mg t.i.d. × 4 wk, then 250 qd. × 4 wk, then doxycycline 100 mg every third day vs. D group: Doxycycline 100 mg q.d. × 4 wk, then 100 every third day × 4 wk, then oxytetracycline 250 q.d.	↓ Total acne load Lesions graded 4 III: I=noninflammatory pustule <double pinhead; II=pustules >grade I with inflammation; III=deep-seated, large infiltrates; Lesions on face, neck, trunk, back counted/graded, given points: grade I = 1 point; II=2 points; III=4 points	After 4 wk: ↓ Total acne load: Both groups ↓ of 45% After 12 wk: T group ↓ of 81%; D group ↓ of 69%
Plewig, 1970 Doxycycline vs. placebo; 62 pts, inflammatory acne	DB, CO Phase I: Doxycycline 100 mg q.d. or placebo × 4 wk, then 4-wk wash-out Phase II: Placebo and doxycycline switched for final 4 wk	Total counts of erythematous papules, pustules, and cysts % ↓ of lesions measured Response scores: Excellent: >75% ↓ lesions Good: 50%–74.9% ↓ Fair: 25%–49.9% ↓ Poor: no change–24.9% ↓ Worsening: ↑ lesions	Phase I: Doxycycline 36% ↓ (p<.001); placebo 12% ↑ Phase II: Doxycycline 24% ↓ (p <.05); placebo 2% ↑ Individual lesion response: Comedones Doxycycline & placebo 76% poor Papules Doxycycline 43% good/excellent; placebo 20% good/excellent Pustules Doxycycline 39% good/excellent; placebo 24% good/excellent Cysts Doxycycline 25% good/excellent; placebo 17% good/excellent
Smith, 1978 Doxycycline vs. minocycline; 30 pts, severe acne	DB, (12 wk Doxycycline (n=8) 100 mg q.d. vs. Minocycline (n=8) 100 mg q.d. Also 5% salicylic acid and 5% resorcinol bid.	Tin lesion score based on: • Extension of ass (grades 1–5, D) • Seborrhea (grades 0–4, S) • Comedones (grades 0–4, C) • Papules & pustules (grades 0–4, P) • Infiltration (grades 0–4, I) • Abscess (grades 0–4, A) (grades not described) Score = E×(S+C+P+I+A) Max=5×(4+4+4+4+4)=100	Doxycycline mean score difference 22.75; Minocycline mean score difference 22.75; not statistically significant
Harrison, 1988 Doxycycline vs. minocycline; 34 acne pts (severity not specified)	Observer-B, 12-wk Doxycycline (n = 15) 50 mg q.d. vs Minocycline (n = 19) 50 mg b.i.d. Also 4% chlorhexidine and 5% benzoyl peroxide	Min=0×(0+0+0+0+0)=0; Change in no. of nodules, pustules, papules on face and back; Weighted scores for active and less active papules=1, pustules=4, nodules=10, cysts=15; Patient assessed severity as a score out of 100 on a 10 cm analog scale; Tolerance of treatment and treatment effect scores 4=excellent, 3=good, 2=fair, 1=poor	↓ Mean total lesion score (adjusted for differences in baseline severity): Doxycycline 66%; minocycline 68% Patient assessment efficacy scores: Doxycycline good/excellent 73%; Minocycline good/excellent 84% Patient tolerance scores: Doxycycline excellent 53%; minocycline excellent 37%
Olafsson, 1989 Doxycycline vs. minocycline; 64 pts, moderate to moderately severe acne	DB, 12-wk Doxycycline (n=33) 50 mg b.i.d. × 4 wk vs. Minocycline (n=31) 50 mg b.i.d. × 4 wk then both q.d. × 8 wk	Lesion counts on head, neck, trunk (papules, pustules, and open comedones [OC] and closed comedones [CC]); Patient and physician assessment of treatment efficacy	90% LESIONS* Doxy / MINO All lesions 56% / 60% Papules 63% / 69% Pustules 64% / 70% OC 42% / 38% CC 43% / 35% Doxy: 85% MDs and pts said rx effective Mino: 87% MDs; 90% pts said rx effective

* P=Percentages based on interpretation of line graphs, exact numbers not given.
DB=double-blind; CO=crossover; P=placebo; sxs=symptoms; chlorhex=; Bs= blind; rx= therapy

Table III. Efficacy of Tetracyclines in Rosacea

Study	Design	Efficacy Measures	Results
Sneddon, 1966 Tetracycline vs. placebo; 78 pts, all degrees of severity	Tetracycline (n=36) 250 mg b.i.d. vs. Placebo (n=42) x 4 wk; then all tetracycline 250 mg b.i.d.	Disappearance of pustules, flattening of papules, diminution of erythema (assessment not described)	After 1 month: Tetracycline 78% improved; Placebo 45% improved After 2nd month: Tetracycline 50% improved; Placebo (now txd with tetracycline) 74% improved
Urabe, 1976 Doxycycline or tetracycline; 9 pts perioral dermatitis (red papules); 16 rosacea-like dermatitis (all stages); 19 rosacea	3-yr period All previously txd topical fluorinated steroids discontinued Doxycycline or tetracycline (dosage not given) for 2–3 mo; concomitant oral prednisolone 5–15 mg qd for 2–3 wk for severe disease; 19 rosacea pts doxycycline 100mg q.d. + topical hydrocortisone x 2 mo	Assessment measures not described	7/9 with perioral dermatitis = healing and full remission 14/16 rosacea-like dermatitis = healing and full remission 14/19 rosacea = clinical improvement 5 = complete cure
Bikowski, 2000 Doxycycline, 2 pts rosacea	2 case reports Pt 1: 100 mg q.d. continued as maintenance Pt 2: 50 mg q.d., reduced to 50 mg q.d. for maintenance	Assessment measures not provided	Pt 1: cleared eruptions in 9 wk. Pt 2: marked ↓ erythema + lesions after 4 wks; in follow-up cleared (time not given). Continued clearing of inflammatory lesions at 6- mo follow-up in both pts
Torresani, 1997 Doxycycline vs. clari; 40 pts	Clari (n=23) 250 mg b.i.d. x 4 wk then 250 mg q.d. x 4 wk vs. Doxycycline (n=17) 100 mg b.i.d. x 4 wk then 100 mg q.d. x 4 wk	Erythema assessed colorimetrics Telangectasias (TAE) color prints and score 0; 1 (<5 TAE nasolabial sulcus); 2 (5–10); 3 (10–20); 4 (20–30 + on chin and forehead); 5 (>30); Pt score efficacy 0 (no efficacy); 1 (low); 2 (traceable); 3 (mild); 4 (good); 5 (high); Tolerability score 0 (no SEs); 1 (occasional); 2 (many sxs); 3 (mild SEs); 4 (sev SEs); 5 (very sev, discont)	After 8 wk: Erythema: mean value Clar: 4.8–5.8 Doxycycline 3.8–5.2 TAEs: ↓ mean score 3.8–2.2 Papules: ↓ mean score 3.8–0.2 Pustules: ↓ mean score 3.8–0.2 Efficacy mean score: Clari: 4.8 Tolerability Doxycycline: 4.2 Clari mean score: 0.32 (occas SEs) Doxycycline mean score: 1.06 (mild SEs)

Clari=Clarithromycin; txd=prescribed; SE=side effect; sev=severe; discont=discontinued

an amino acid side chain with potential to form a reactive metabolite. Neither tetracycline HCl nor doxycycline contains the amino acid side chain; therefore, the hypersensitivity reactions associated with minocycline may be specific to this antimicrobial.[28] In vitro studies have demonstrated the presence of a minocycline-glutathione conjugate when minocycline is incubated with hypochlorous acid, as is found in neutrophils. When a reactive metabolite is generated, glutathione transferase acts to detoxify this product. The presence of minocycline-glutathione conjugates implies the formation of potentially toxic metabolites. These potentially reactive metabolites generated by minocycline may bind to tissue macromolecules causing cell damage directly, or they may act as haptens, eliciting a secondary immune response.[29]

Adverse Events Associated With Acne Therapy

Tetracyclines as a Class of Antimicrobials. GI disturbances (nausea, vomiting, and diarrhea) are the most common side effects associated with all the tetracyclines. All tetracycline antimicrobials carry warnings of phototoxicity reactions, manifested as an exaggerated sunburn reaction. To date, there have been no double-blind, controlled studies showing that tetracycline HCl is a photosensitizer. Minocycline is generally regarded as the least photosensitizing of the tetracycline derivatives at the commonly administered dose.[30]

Prescribing information for all tetracyclines warns that they can cross the placenta and have shown evidence of embryotoxicity with

toxic effects on the developing fetus. Minocycline has been shown to have a carcinogenic metabolite, although the clinical relevance of this finding is unknown.[31]

Tetracycline HCl. Tetracycline HCl has been implicated in an increased incidence of esophageal ulceration,[32] particularly when administered in capsule form. The use of tetracycline HCl has also been associated with the development of pseudotumor cerebri in adult and pediatric patients[33] and in patients receiving concomitant isotretinoin therapy.[34]

Doxycycline. Esophageal irritation has been seen with doxycycline hyclate, which dissolves at a pH of 2–3. In contrast, the pH on dissolution of the newer salt, doxycycline monohydrate, is 5–6, resulting in no esophageal irritation and less GI upset.[15]

Photosensitivity can be seen with doxycycline therapy. The relationship is dose dependent, and phototoxicity occurs in 3% of patients taking 100 mg/day. This can be a problem clinically because patients who do not respond to standard doses may be taking maintenance therapy doses in excess of 100 mg/day, which greatly increases the potential for phototoxic eruptions (20% at 150 mg and 42% at 200 mg/day).[35]

Because these drugs are given long-term for acne and rosacea, the possibility for carcinogenic potential is also of concern. Recently, during the development of a SD of doxycycline as a chronic, adjunctive therapy for the treatment of adult periodontitis, this issue was systematically addressed for the first time. The labeling for this drug (Periostat) states that the carcinogenic potential of doxycycline has been investigated with no findings of changes indicating a direct carcinogenic effect. Increases in benign fibroadenomas of the breast, polyps of the uterus, and adenoma of the thyroid, which are consistent with a hormonal effect, were observed in treated women. Doxycycline has shown no mutagenic activity and no convincing evidence of clastogenic activity.[36]

Minocycline. The vestibular side effects of lightheadedness, loss of balance, dizziness, or true vertigo in patients taking minocycline are well known and occur more often in women.[37,38] These effects arise because the lipophilicity of minocycline results in some degree of blood-brain barrier penetration.

Hyperpigmentation or a blue/black skin or mucous membrane discoloration has been found with long-term use of minocycline.[39,40] In rare cases, such hyperpigmentation may occur within 1 month of minocycline therapy. There are two types: localized pigmentation occurring at the site of previous inflammation, and a more generalized diffuse pigmentation.[41]

Although rare, a variety of drug-induced syndromes have been described in patients taking minocycline for acne. Drug-induced lupus and hepatitis are the most common reactions and except for serum sickness (mean time to occurrence: 16 days); these syndromes typically present after prolonged use (mean time to occurrence: 25.3 months).[42,43] Coexistent minocycline-induced lupus erythematosus and autoimmune hepatitis after long-term use (4–120 months) occurred at dose ranges of 50–200 mg/day.[44] Hepatitis with minocycline use is most often associated with hypersensitivity syndromes or delayed autoimmune hepatitis.[44,45]

Case reports of pneumonitis,[46] lymphadenopathy, and an infectious mononucleosis-type reaction[47] have been reported. Rare cases of pseudotumor cerebri (idiopathic intracranial hypertension)[48] associated with long-term minocycline treatment (4 weeks–18 months) have occurred.[41,49] Long-term administration in rat studies resulted in evidence of thyroid tumor production and thyroid hyperplasia in rats and dogs.[31] Based on reports of adverse drug reactions, Gough et al.[50] recommended that safer alternatives than minocycline should be considered for treating acne.

A New Therapeutic Option—SD Doxycycline

Within a decade of their discovery in 1947, tetracyclines were widely used as anti-infectives and for the treatment of acne.[51] Steadily increasing rates of bacterial resistance limited their use for many infections. In 1983, Golub reported on a seminal study in rats in which minocycline inhibited tissue collagenolytic enzyme activity by mechanisms independent of its antibacterial activity.[52] This finding spawned an extensive series of experiments to elucidate the nonantimicrobial properties of tetracyclines, suggesting a new therapeutic

potential for the tetracyclines. This promoted a renewed interest in this class of drugs.

Nonantimicrobial Properties of Tetracyclines. Much of the early research investigating the nonantimicrobial potential of the tetracyclines was done in the treatment of adult periodontitis.[53] The tissue and bone degrading characteristics of periodontitis involve a prolonged and excessive host inflammatory response to the presence of bacteria, which promotes the activity of matrix-degrading metalloproteinases (MMPs), as well as alterations in the metabolism of bone. MMPs are proteolytic enzymes produced by infiltrating inflammatory cells and resident connective tissue cells. These enzymes induce the excessive degradation of collagen, the primary structural component of the periodontal matrix. In combination with alterations in the relative capability of the tissues to form new bone, particularly in patients with certain specific risk factors and underlying systemic disease processes, this ultimately leads to the net loss of connective tissue attachment and supporting alveolar bone, the latter being the signature event of periodontitis.[54] In vivo and in vitro studies in humans and animals found that tetracyclines can independently inhibit MMP activity and stimulate new bone formation, thereby preventing connective tissue breakdown and contributing to the prevention of net alveolar bone loss.[53]

Tetracyclines inhibit connective tissue breakdown by several mechanisms, directly and indirectly, depending on the particular status of the tissues involved and the stage of disease progression. They directly inhibit active MMPs, such as MMP-8, MMP-9, and MMP-13, as well as the oxidative activation of pro-MMPs. They disrupt MMP activation by promoting excessive proteolysis of pro-MMPs into enzymatically inactive fragments. This inhibition of MMPs protects α-$_1$ proteinase inhibitor (α-$_1$-PI), the major endogenous inhibitor of serine proteinases, and another class of tissue destructive enzymes. Protection of α-$_1$-PI indirectly decreases the tissue activity of serine proteinases, and protects the endogenous levels of the naturally occurring MMP inhibitors known as the Tissue Inhibitors of Matrix MetalloProteinases. Tetracyclines also down-regulate the expression of proinflammatory mediators, including cytokines such as interleukin-1 and TNF-α, thereby inhibiting extracellular matrix breakdown.[53]

Use of Subantimicrobial Doses. Long-term therapy using standard antimicrobial doses of tetracyclines for chronic disorders such as periodontitis was not widely accepted due to the potential development of microbial resistance in the bacterial flora of the exposed population and other risks of side effects associated with long-term administration of tetracyclines. Studies suggested that these issues could be overcome by using tetracycline regimens that maintained blood levels below those purported to result in antimicrobial activity at the site of infection.[53,55]

Doxycycline was chosen over other tetracyclines for these studies because it was found to be the most potent inhibitor of MMP activity amongst the commercially available tetracyclines, and the best tolerated from the perspective of long-term administration.[56] Extensive preclinical and early-stage clinical work established a dosing regimen (20 mg twice daily) which was effective at down-regulating MMP activity and a variety of proinflammatory cytokines induced by infecting bacteria *without* producing a detectable effect on the microflora (e.g., decreased microbial counts).[53,57,58] The success of these initial investigations led to longer-term, randomized, placebo-controlled, multicenter, double-blind clinical trials in adult periodontitis (AP). One early study in a population with AP suggested that SD doxycycline 20 mg twice daily suppresses collagenase activity in the periodontal pocket.[58] The dose was low enough to avoid any impact on the oral microflora yet sufficient to inhibit host collagenase activity in gingival crevicular fluid by 40%–50%.[58]

Lack of Antimicrobial Effect of SD Doxycycline. Microbiological testing was an important part of the study designs for the pivotal trials to establish the safety and efficacy of SD doxycycline (20 mg twice daily) for AP. This dosing regimen provided the maximum dose that achieved plasma concentrations consistently well below those required for an antimicrobial effect and resulted in maximum steady state plasma concentrations of 0.79 μg/mL after approximately 1.5 hours.[36]

One 9-month study compared SD doxycycline to placebo, evaluating the antimicrobial effect on subgingival microflora. There were no differences between or within the 2 treatment groups detected in any of the microbiologic

parameters, with the exception of a decrease in the proportion of spirochetes ($p<0.05$).[59] Clinical trials for SD doxycycline in periodontitis demonstrated no effect on total anaerobic or facultative bacteria in plaque samples from patients given SD doxycycline for 9–18 months.[36] In long-term studies of SD doxycycline (open-label, blinded, controlled studies), MIC levels for organisms remained constant among all treatment groups compared with baseline at 18 and 24 months. There were no statistically significant differences in the proportion of doxycycline-resistant isolates among treatment groups and no evidence of multi-antimicrobial resistance or cross-resistance at any time point.[60]

> "Microbiological testing was an important part of the study designs to establish safety and efficacy of SD doxycycline (20 mg twice daily)"

Long-term clinical studies in patients receiving SD doxycycline for up to 18 months confirmed the clinical efficacy in treating AP with no evidence of effects on the microflora of the oral cavity or GI tracts.[53,61,62] The incidence of adverse events was minimal, comparable to placebo, suggesting that the adjunctive use of SD doxycycline was a clinically important strategy for the management of AP with a high benefit/risk ratio. Based on these clinical trials SD doxycycline was approved by the Food and Drug Administration (FDA) in 1998 for up to 12 months use in the adjunctive treatment of periodontal disease.

Use of SD Doxycycline in Acne

Although tetracyclines at antimicrobial doses (1 g/day) are routinely used for the treatment of acne, the need for long-term therapy increases the risk of adverse events, drug interactions, and the emergence of resistant strains of microorganisms. The carcinogenic potential, effects on reproduction, and long-term sequelae of such regimens have not been explored in long-term clinical trials. Tetracyclines are FDA-approved only for short-term use in the adjunctive treatment of severe acne, and not at all for the treatment of rosacea.

The lesions of inflammatory acne are mediated by an inflammatory host response somewhat similar to that observed in chronic AP, at least in terms of neutrophil infiltration and expression of inflammatory cytokines.[63] Based on the success in the treatment of AP using SD doxycycline, it was postulated that the nonantimicrobial properties of doxycycline at the SDs of 20 mg twice daily may be effective at managing the signs and symptoms of acne. Refer to Table IV for a comparative summary.

Doxycycline's effect on inflammatory acne may be due, in part, to the drug's ability to inhibit lipase production by *P. acnes*.[64] Doxycycline down-regulates IL-8, IL-1β, and TNF-α, which potentiate the inflammatory pathway and lead to further recruitment of cellular components, such as PMN-derived collagenase (MMP-8).[53] It also inhibits production of chemotactic factors, which attract neutrophils to the follicular lumen, at drug concentrations that do not inhibit the organism.[64,65]

Skidmore et al.[66] have conducted the first double-blind, placebo-controlled, long-term trial comparing the efficacy and safety of SD doxycycline (20 mg twice daily, 6 months) in acne. Of the 51 patients originally entered, 40 completed the study and satisfied the criteria for efficacy analysis. The group receiving SD doxycycline had a significantly greater percent reduction in the number of comedones ($p<0.01$), total inflammatory lesions, ($p<0.05$) and all lesions combined at 6 months. The clinician's global

Table IV. Comparative Summary of Periodontal Disease vs. Acne

PERIODONTITIS	ACNE
Anaerobic bacteria (e.g., *Porphyromonas gingivalis*) in the periodontal pocket induce a host inflammatory response	Trapped *Propionibacterium acnes* induce an inflammatory host response
Inflammatory host response results in clinical signs and symptoms of disease • Gingival inflammation • Periodontal pocketing • Bone loss	Inflammatory host response results in clinical signs and symptoms of disease • Papules • Pustules • Nodules
Certain patients are more susceptible than others • Genetic component	Certain patients are more susceptible than others • Genetic component

assessment also showed a significantly greater improvement with SD doxycycline (20 mg twice daily) at 6 months ($p<0.05$).

There were no significant differences in the cutaneous microbial counts and no evidence of the emergence of resistant organisms in either group. Furthermore, the dose was well tolerated with no evidence of drug-related adverse events such as nausea, vomiting, phototoxicity, or vaginitis.[66]

SD Doxycycline in Adult Rosacea

Based upon the known features and diagnostic criteria of rosacea, this author hypothesized that the SD of doxycycline would also be effective for the treatment of rosacea. If effective, this would provide an important treatment option for rosacea patients who often require long-term tetracycline therapy to avoid recurrence. Such long-term uses place this patient group at risk for uncomfortable and potentially severe side effects.[67] The use of SD doxycycline would also alleviate the concern of emerging microbial resistance.

In this open-label study of 50 rosacea patients, all stages of rosacea were included to assess the effects of SD doxycycline in treating the various signs and symptoms associated with each stage. To ensure pure evaluation results, patients were only treated with SD doxycycline (20 mg twice daily) and no other oral or topical agents were prescribed. In addition, most patients were virgin cases who had never received treatment for their rosacea symptoms.

Patients were evaluated at the initial visit and again between 2 and 8 weeks for erythema, inflammatory lesions, and telangiectasias.

Based upon subjective and objective findings, clinical efficacy achieved with SD doxycycline was very similar to results usually seen with standard antibiotic dosages of tetracyclines when used monotherapeutically, and consistent with the limited literature in this area. After an average of 4 weeks of treatment with SD doxycycline twice daily, patients experienced an 80%–100% clearing of inflammatory lesions and a 50% reduction in erythema (Figures 1 and 2). A decrease in the size and diameter of telangiectatic vessels was also observed, although complete clearing of the telangiectasias was not achieved. Consistent with previous study results of SD doxycycline, there were no reports of nausea, vomiting, headache, diarrhea, vaginitis, or photosensitivity (including those patients with documented histories of such adverse reactions on higher doses of doxycycline).

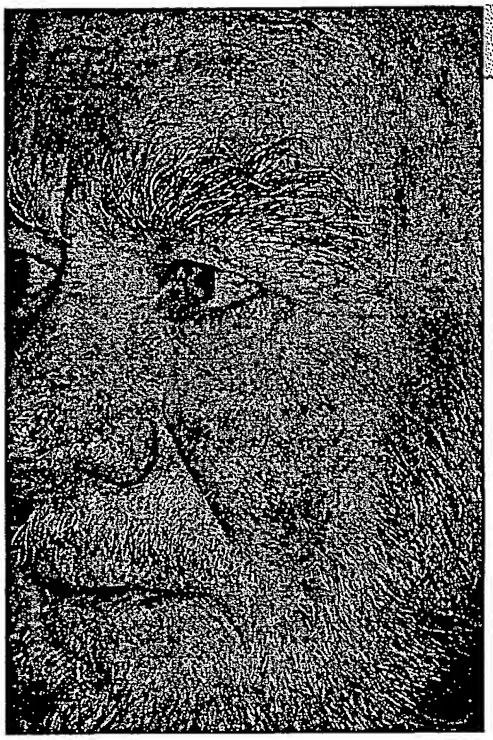

Figure 1. Patient with moderately severe rosacea at baseline.

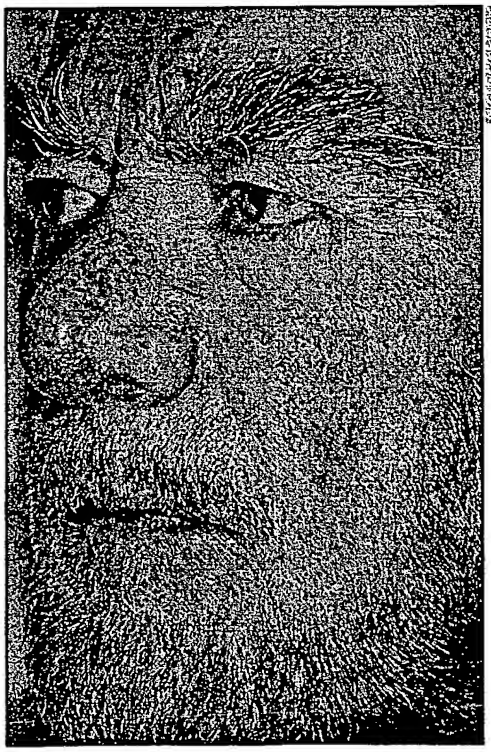

Figure 2. Eight weeks post treatment with monotherapy using SD doxycycline 20 mg given by mouth twice daily.

Conclusions

The tetracyclines have been used effectively for decades for the treatment of acne and

rosacea at doses of 50–200 mg daily for doxycycline and minocycline and 250 mg twice or four times daily for tetracycline HCl. Reports of serious adverse events and the increasing rates of bacterial resistance to tetracyclines at standard doses in patients undergoing long-term therapy have prompted interest in new therapeutic approaches for their use in acne and rosacea therapy.

Lesions of periodontitis and acne are mediated by a somewhat similar inflammatory response. The efficacy of clinical trials and subsequent approval of SD doxycycline in adult periodontitis was the impetus for the study of its effect in acne. Results from the study of SD doxycycline in acne are promising and should encourage further research into this new strategy for treating acne. A 50-patient, open-label experience trial with SD doxycycline in the treatment of rosacea also provided evidence of the utility of the drug. The use of SD doxycycline can potentially avoid the adverse events of standard-dose, long-term therapy with tetracyclines for acne and thereby enhance patient compliance. In addition, widespread adoption of this dosage as part of a maintenance therapy for acne and rosacea will limit exposure of patients and their microflora to doxycycline and may slow the steadily increasing rate of resistance of *P. acnes* and other organisms to the tetracyclines.

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